GI Lymphomas

with a focus on gastric MALT lymphoma

Abdul Al-Tourah, M.B., B.Ch.

Medical Oncologist

BCCA-Fraser Valley Centre

Clinical Assistant Professor of Medicine

UBC

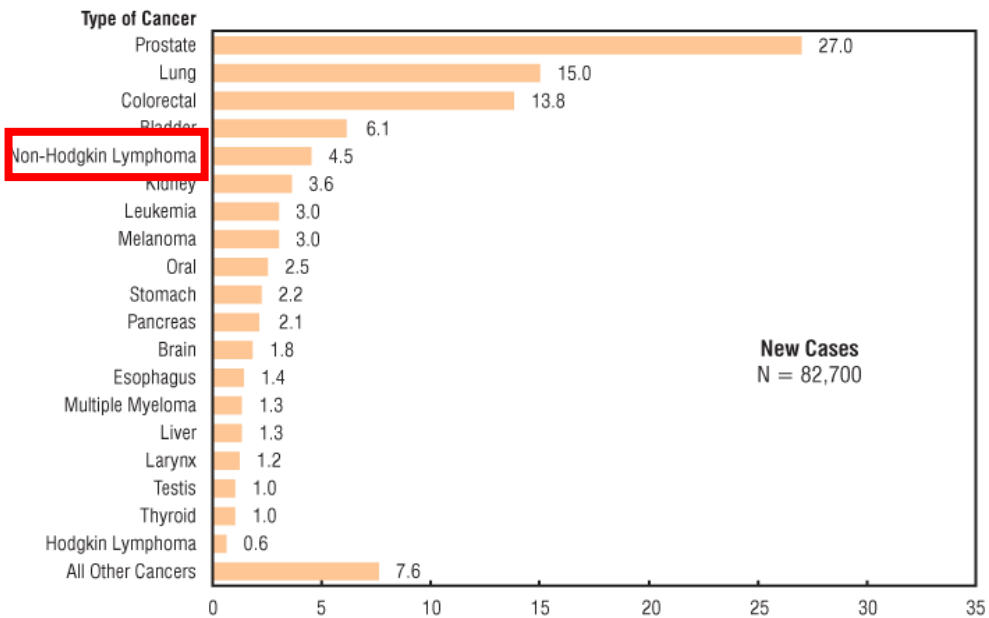
Learning Objectives

- Understand the current trends in incidence of Non-Hodgkin Lymphoma
- Understand initial evaluation of newly diagnosed patient
- Current management of gastric MALT lymphoma
- Brief review of other types of GI lymphomas

Non-Hodgkin Lymphoma
Canadian Cancer Statistics 2007

Figure 1.1

Percentage Distribution of Estimated New Cases for Selected Cancers, Males, Canada, 2007



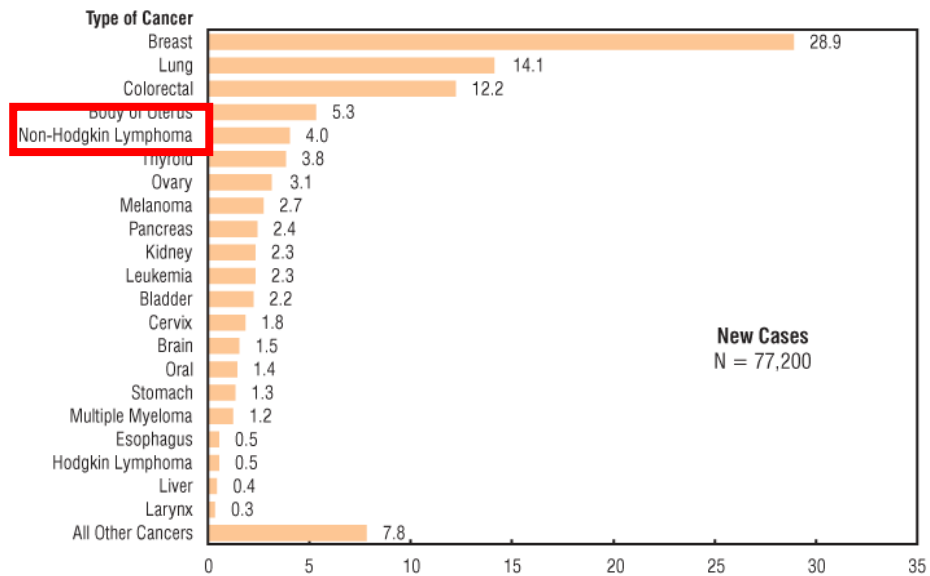
Note: Incidence figures exclude an estimated 69,000 new cases of non-melanoma (basal cell and squamous cell) skin cancer among both sexes combined. Mortality figures for 'all other cancers' include about 220 deaths with underlying cause 'other malignant neoplasms' of skin among both sexes combined.

Source: Surveillance Division, CCDPC, Public Health Agency of Canada

Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2007*

Figure 1.2

Percentage Distribution of Estimated New Cases for Selected Cancers, Females, Canada, 2007



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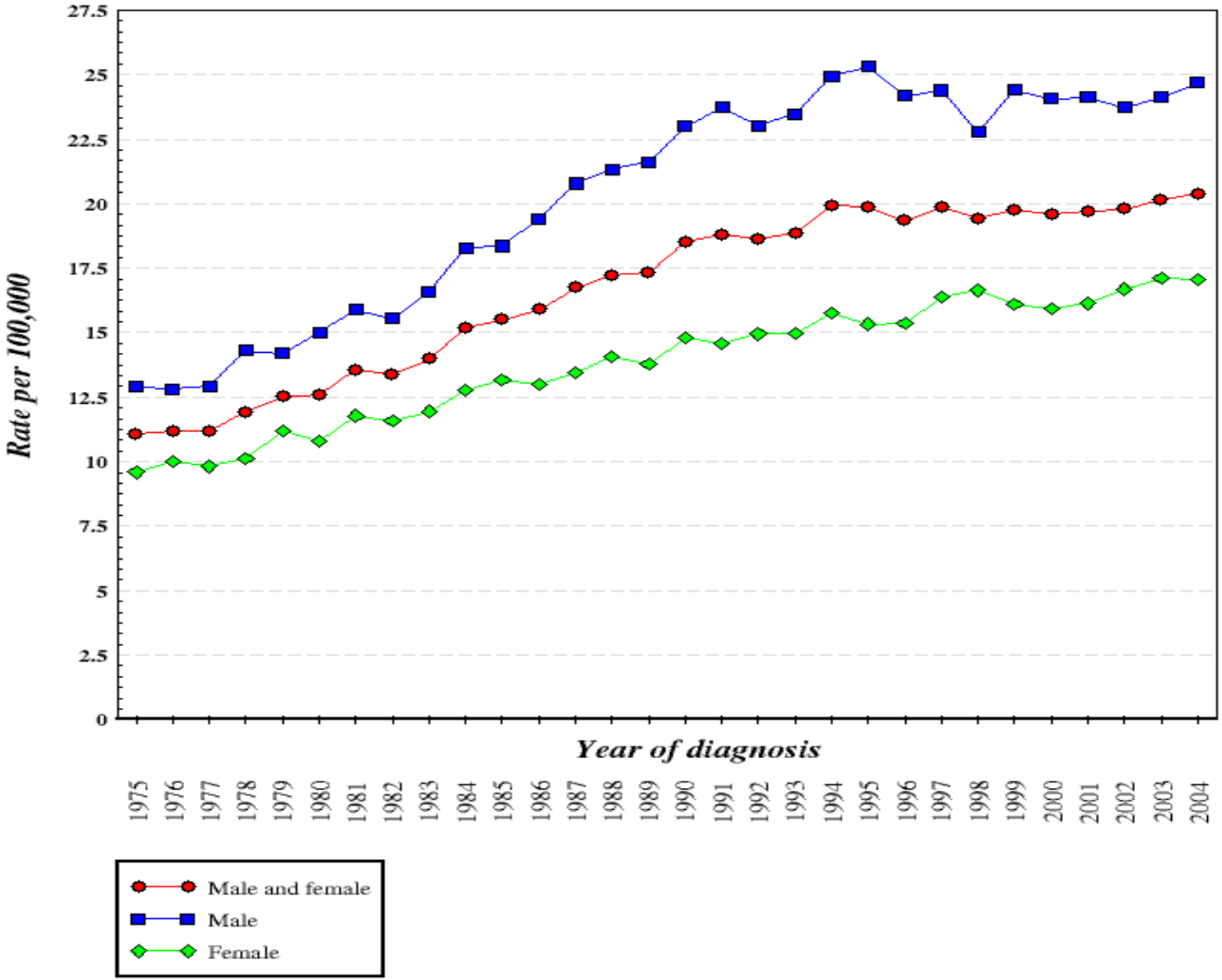
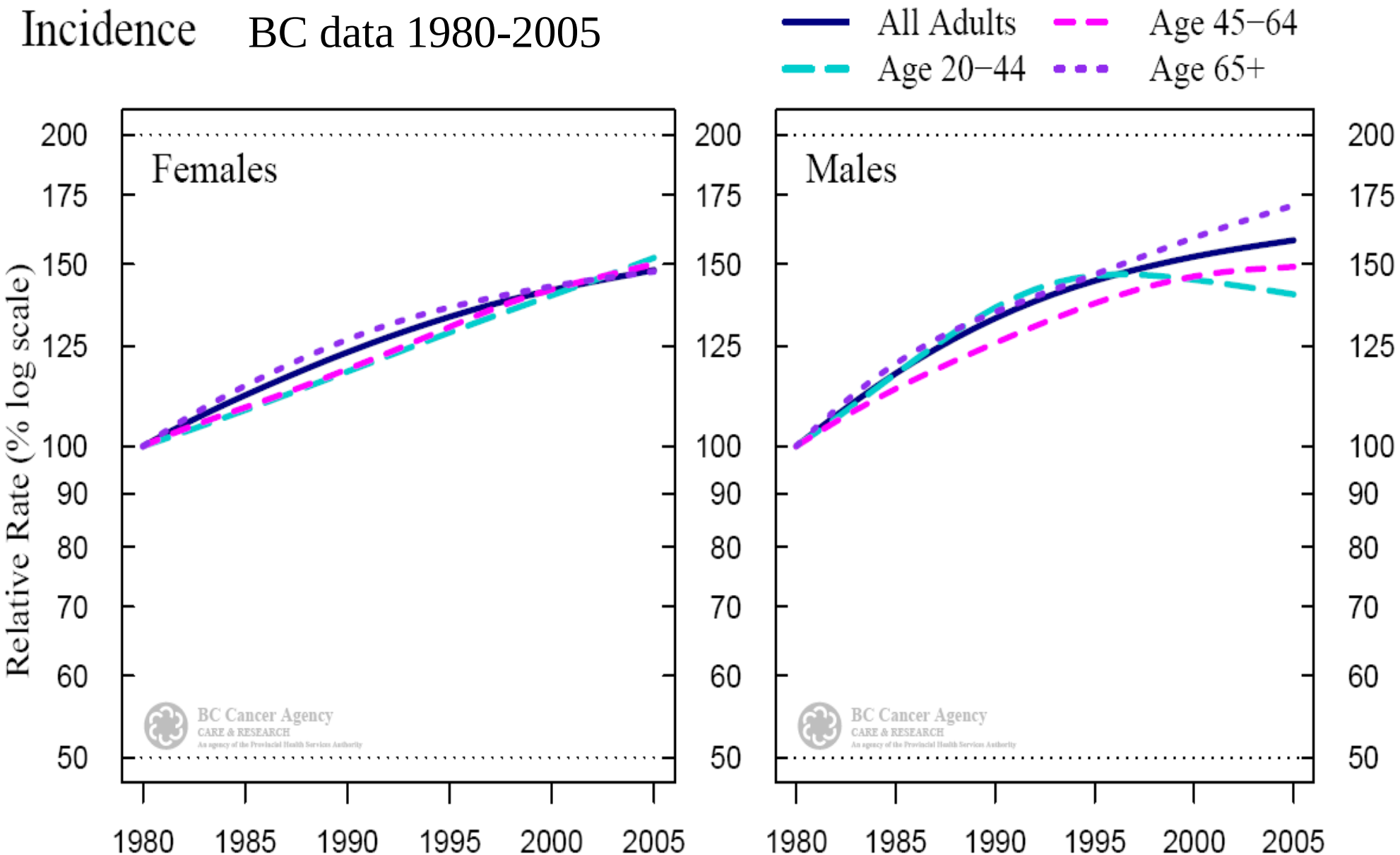
NHL increasing incidence SEER 1975-2004 (age-adjusted)



Non−Hodgkin Lymphoma

Incidence BC data 1980-2005



Initial Evaluation of Lymphoma Patient

- History , B symptoms (fever, night sweats, weight loss)
- Physical exam
- Labs: CBC, LDH, LFT
- CT scan neck, chest, Abdomen and pelvis
- Bone marrow biopsy
- Review of diagnostic material by an expert lymphoma pathologist
- GI lymphoma, ENT evaluation for Waldeyer’s ring (20%)

Pathological diagnosis of lymphoma

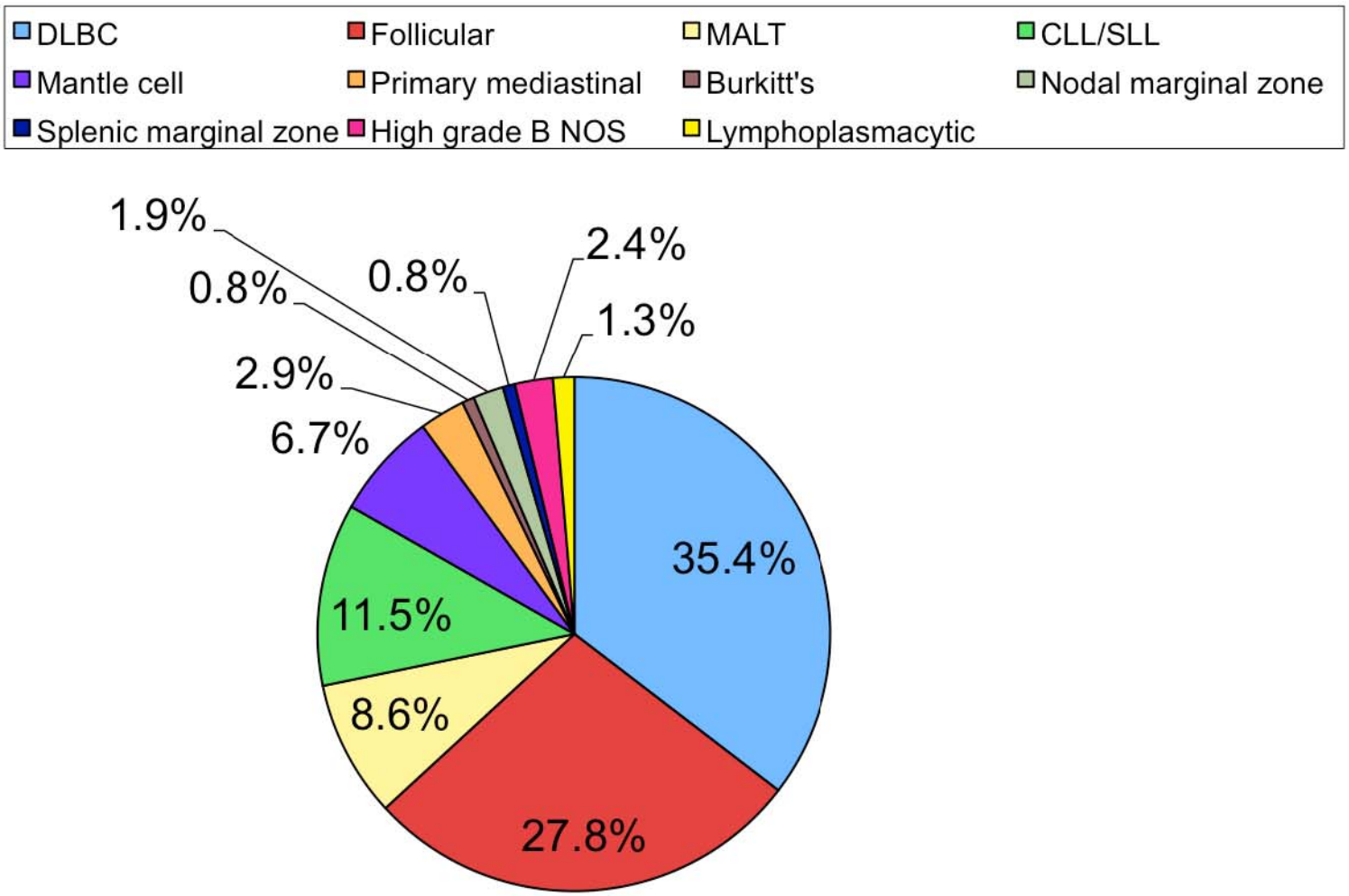
- Assessment of nodal architecture is Key to making the correct diagnosis and classification of lymphoma
- Not a cytological disease
- Should not relay on FNA biopsy for treatment
- Core biopsy (multiple) is superior to FNA but crush artifacts can make interpretation difficult
- Adequate tissue is important for special tests e.g. cytogenetics

FNA to diagnose lymphoma
Univ of Arizona series n=95

FNA diagnosis	**%**
NHL with subtype	29
NHL no subtype	18
Atypical	16
Suspicious	10
Non-diagnostic	14
normal	3

Frequency of B-cell lymphoma subtypes

(WHO Classification of Tumours, 2008)



Lymphoma and the GI tract

- Primary GI lymphoma
  - GI tract clinically dominant extra-nodal component after careful staging (no or minor nodal involvement)
- Secondary GI involvement
  - GI tract is involved as part of more wide spread nodal disease

Primary Extranodal Lymphomas

- Extranodal presentation accounts for 24-48% of all new lymphoma cases
  - North America 27%
  - Italy 48%
  - The Netherlands 41%
  - Hong Kong 29%
- Primary GI lymphoma most frequent, 20-30%

Primary GI Lymphomas

- B-cell
  - MALT (indolent, low grade)
  - DLBCL (aggressive, intermediate grade)
  - Follicular (indolent)
  - Mantle cell (aggressive)
  - Burkitt’s (high grade)
- T-cell
  - Enteropathy associated T-cell lymphoma

German Study of 370 with GI lymphoma

- Stomach — 75 percent
- Small bowel (including duodenum) — 9 percent
- Ileo-cecal region — 7 percent
- More than one GI site — 6 percent
- Rectum — 2 percent
- Diffuse colonic involvement — 1 percent

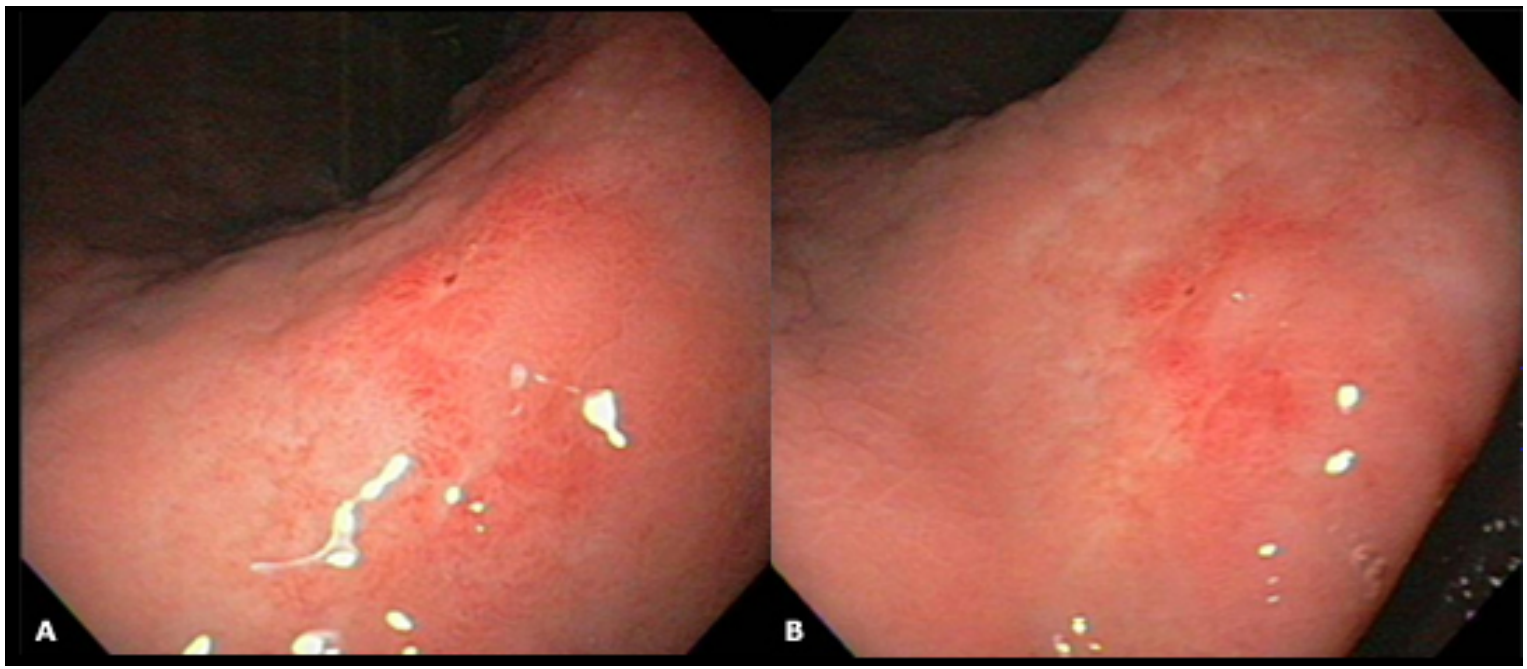
Symptoms at diagnosis, n= 185

Symptoms*	No.	%
Pain	149	80.5
Loss of appetite	66	46.5
Loss of weight†	43	23.2
Vomiting	35	18.9
Bleeding	30	16.0
Night sweats	21	11.4
Diarrhea	8	4.3
Constipation	8	4.3
None	8	4.3
Perforation	5	2.7
Fever	4	2.2
B symptoms (fever, night sweats)	22	11.9

Koch, P. et al. J Clin Oncol; 19:3874-3883 2001

Gastric MALT Lymphoma

(Extranodal Marginal Zone B-cell lymphoma of Mucosa-Associated Lymphoid Tissue)



Upper endoscopy showing a superficial ulceration with mucosal thickening in the incisura with surrounding erythema. ***Courtesy of John K. Kwon, MD and Harry Anastopoulus, MD.***

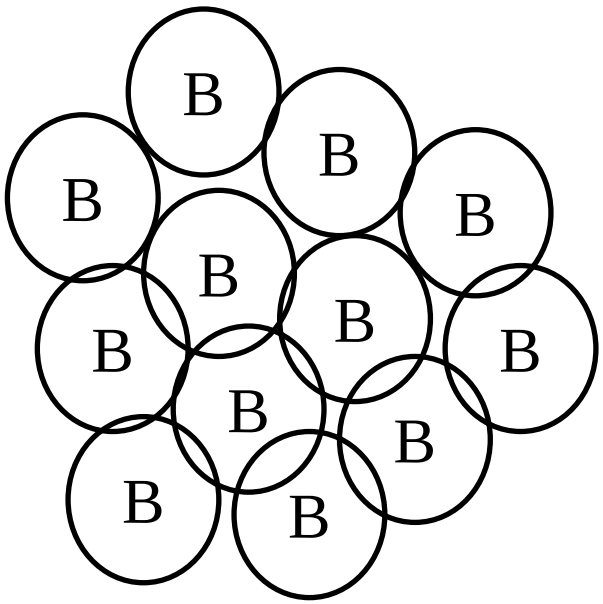
Gastric MALT

- Stomach most common site of GI MALT (85%)
- 6% of all B-cell lymphomas
- Median age 60 yrs
- Male:female 1:1.2
- Majority localized (stage I or II);
- bone marrow involvement rare <15%

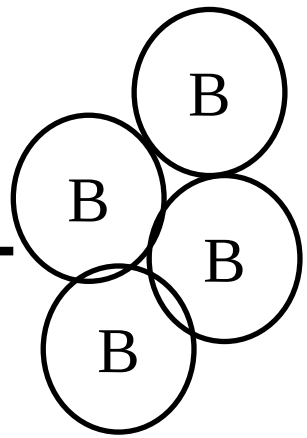
H. Pylori and gastric MALT lymphoma timeline

- 1982 Marshall et al linked H.pylori with gastritis/ulcers
- 1983 Isaacson and Wright describe MALT lymphoma
- 1991 90% prevalence of H. pylori in gastric MALT
- 1992 Greater incidence of gastric MALT in northern Italy (13.2 per 100,000) where H. pylori has highest prevalence
- 1993 Gastric MALT cells exhibit an immune response to H. pylori
- 1993 First cases of regression of MALT lymphoma with treatment of H.pylori
- 1995 First trial confirming anti-H.pylori therapy leads to regression of lymphoma

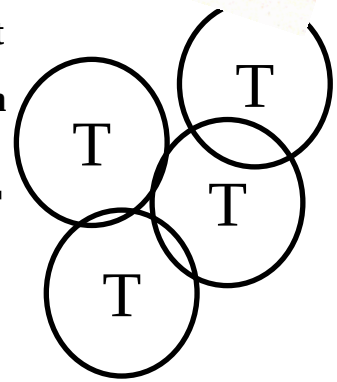
H. Pylori and Pathogenesis of gastric MALT lymphoma



genetic alterations



Contact dependent B-cell proliferation



H. Pylori dependent MALT lymphoma 75%

B-cell proliferation

Mucosal T-cell proliferation

H. Pylori independent MALT lymphoma

further genetic alterations

Transformed MALT lymphoma (aggressive)

Surgical treatment of gastric MALT

- Surgical resection alone for stage I 85-95% disease free survival [1,2]
- But total gastrectomy is needed due to the multifocal nature of gastric MALT
- Less invasive treatments offer similar results e.g. antibiotics, chemotherapy and radiation

1. Cogliatti et al Gastroenterol 1991, 2. Ruskone-Formestraux et al Gastroenterol 1991

Radiation alone for stage I/II gastric MALT
MSKCC experience 17 patients

- 17 pts without H. pylori infection or persistent MALT despite antibiotics
- RT: 30 Gy (1.5 Gy in 4 weeks to stomach and regional nodes)
- 100% biopsy confirmed complete response rate (median f/u 2 years)

Schechter et al JCO 1998

Survival of patients with stage IAE gastric MALT by treatment modality

Treatment	n	CR rate	5-year OS
Antibiotics	45	67%	94%
Local therapy [a]	14	100%	92%
Chemo	8	50%	75%
Combined [b]	5	100%	80%
Total	72	74%	89%

a surgery +/- Radiation; **b** surgery+ chemo

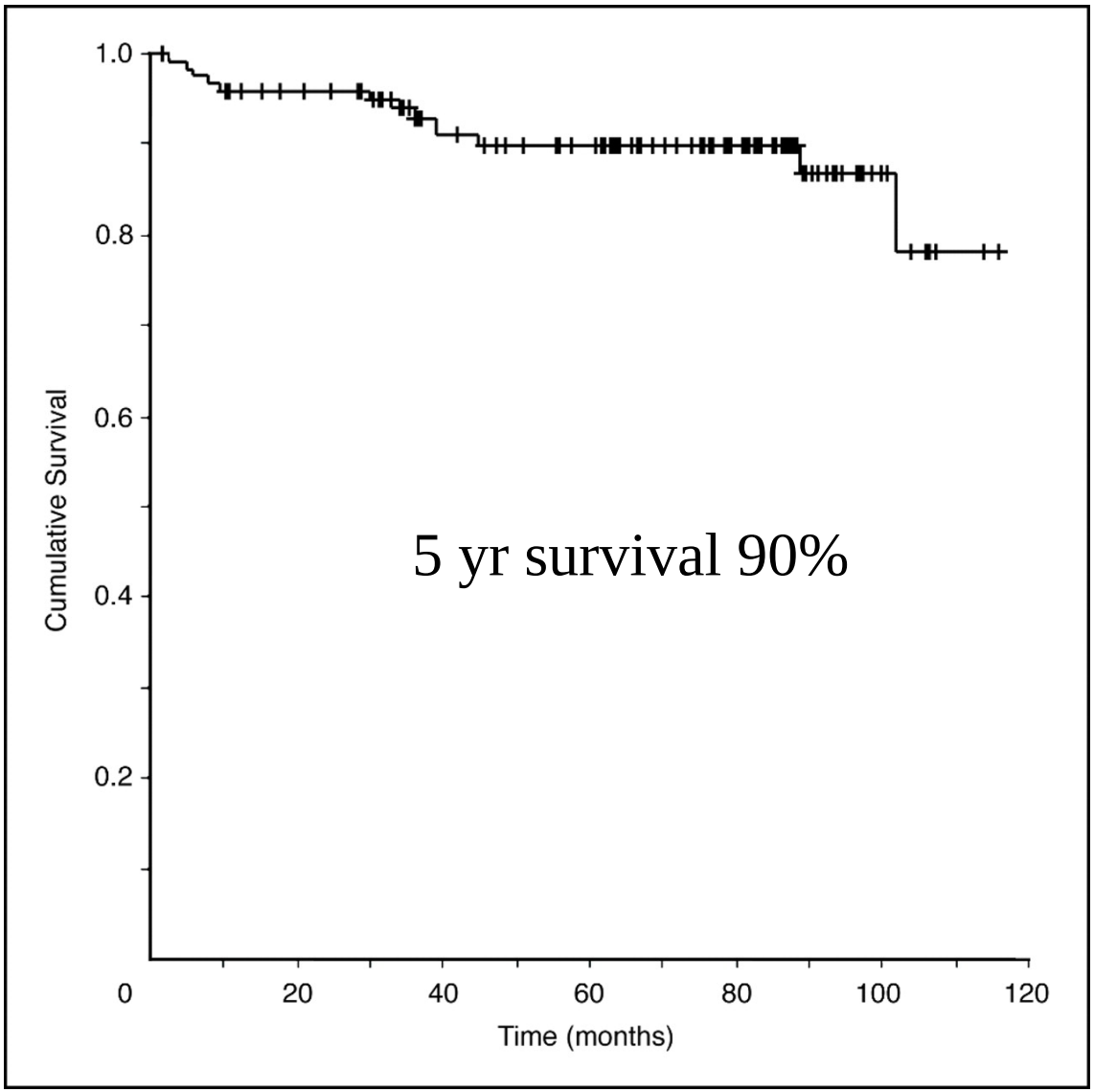
Pinotti et al, Leuk Lymphoma 26:527-537, 1997

Response to Antibiotics in stage IE gastric MALT

Author	n	CR rate (%)	Time to CR (months)	Relapses (%)
Savio,1996	12	84	2-4	0
Pinotti, 1997	45	67	3-18	4
Neubauer, 1997	50	80	1-9	10
Nobre Leitao, 1998	17	100	1-12	6
Steinbach, 1999	23	56	3-45	0
Montalban, 2001	19	95	2-19	0
Ruskone, 2001	24	79	2-18	11
Bertoni, 2002	189	55	-	14

CR= complete response

Overall survival of gastric MALT pts After *Helicobacter Pylori* eradication, N=120



Wündisch T et al. JCO 2005;23:8018-8024

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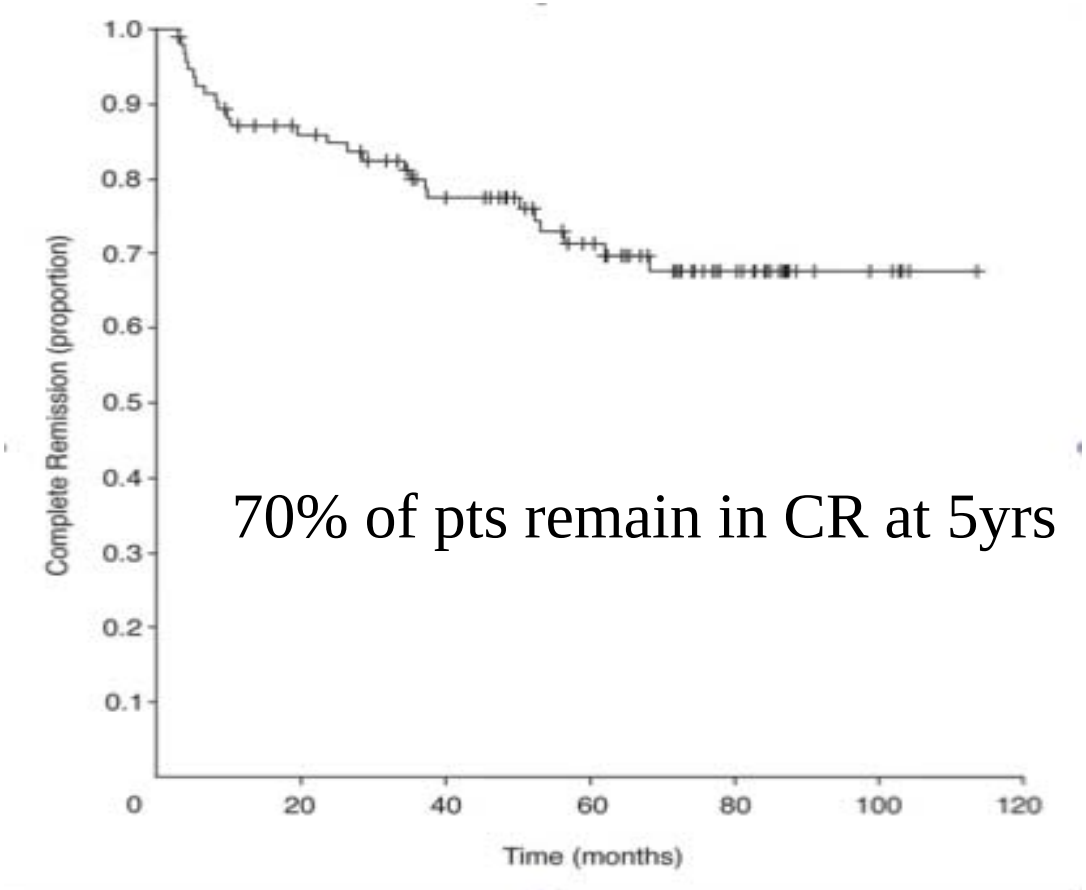
Duration of complete remission of gastric MALT Lymphoma After *Helicobacter Pylori* Eradication N= 96



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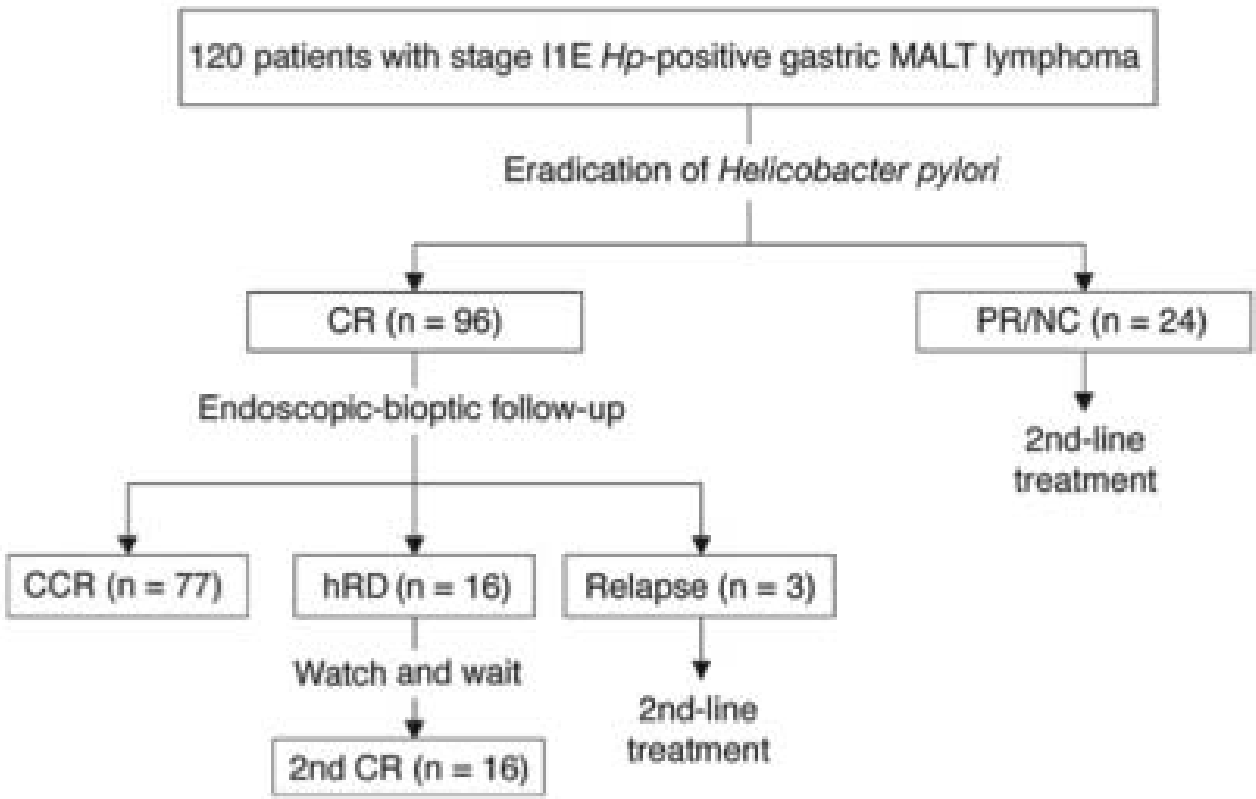
Long-term follow-up of gastric MALT after HP eradication



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Predictive Role of Endoscopic US

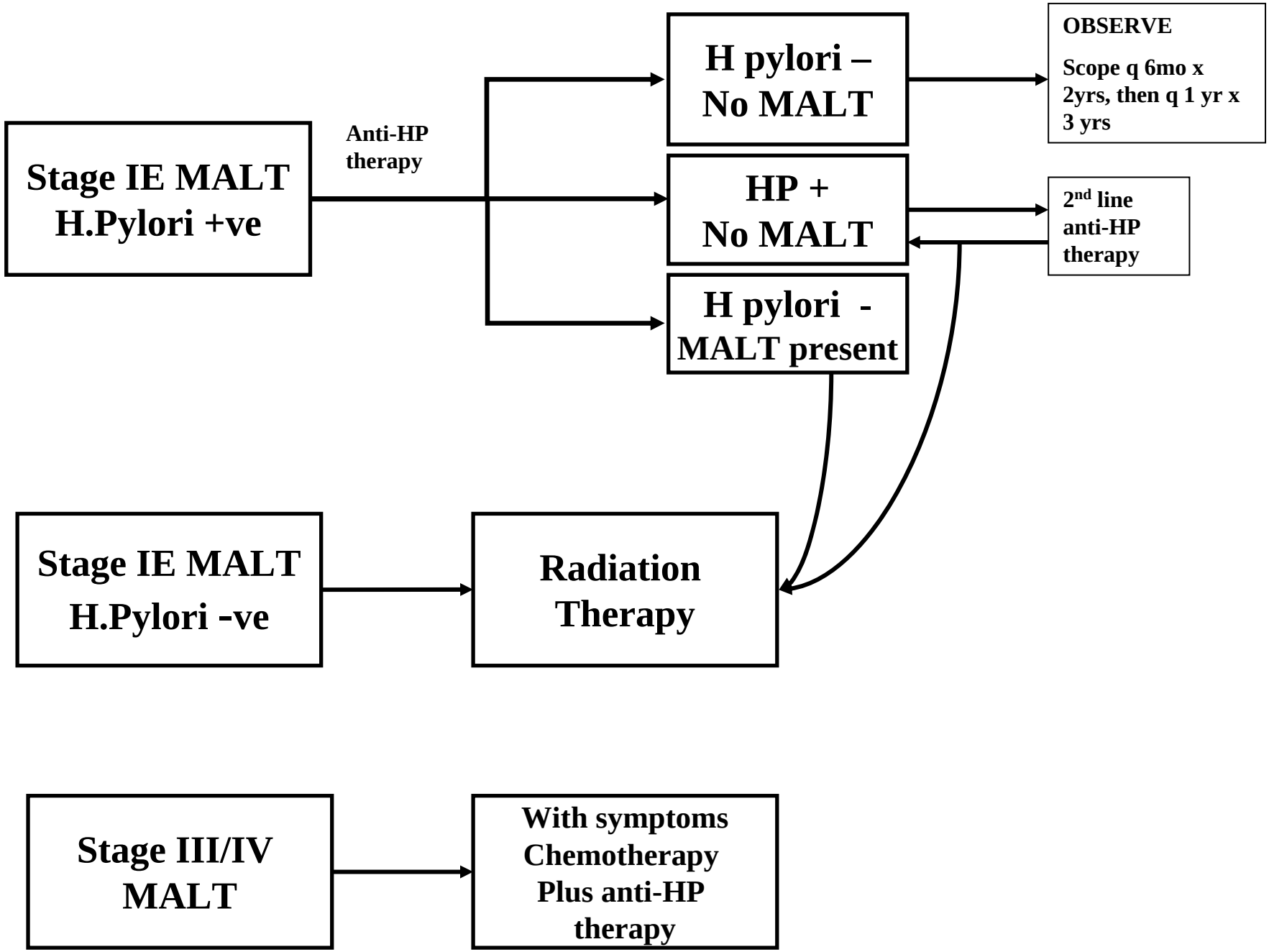
34 gastric MALT lymphoma cases

Depth of invasion	# pts achieving complete response	Complete response rate %
Mucosal	14/18	78%
Submucosa	3/7	43%
Muscularis propria	1/5	20%
Serosa	1/4	25%

Ruskone-Formestraux et al 2001

Predictors of poor response to antibiotic therapy

- Absence of *Helicobacter pylori* infection
- Regional nodal involvement
- Tumour infiltration beyond the mucosa
- Presence of high grade lymphoma component
- Chromosomal translocation, t(11;18)


Stage IE MALT
H.Pylori +ve
Anti-HP
therapy
H pylori –
No MALT
HP +
No MALT
H pylori -
MALT present
OBSERVE
Scope q 6mo x
2yrs, then q 1 yr x
3 yrs
2nd line
anti-HP
therapy
Stage IE MALT
H.Pylori -ve
Radiation
Therapy
Stage III/IV
MALT
With symptoms
Chemotherapy
Plus anti-HP
therapy

MALT lymphoma of Stomach

- Post- treatment surveillance (BCCA guidelines):
  - After completion of treatment repeat gastroscopy every 6 months for 2 years then annually for 3 years
  - Random biopsies from GE junction, stomach and duodenum and of any detected abnormality.

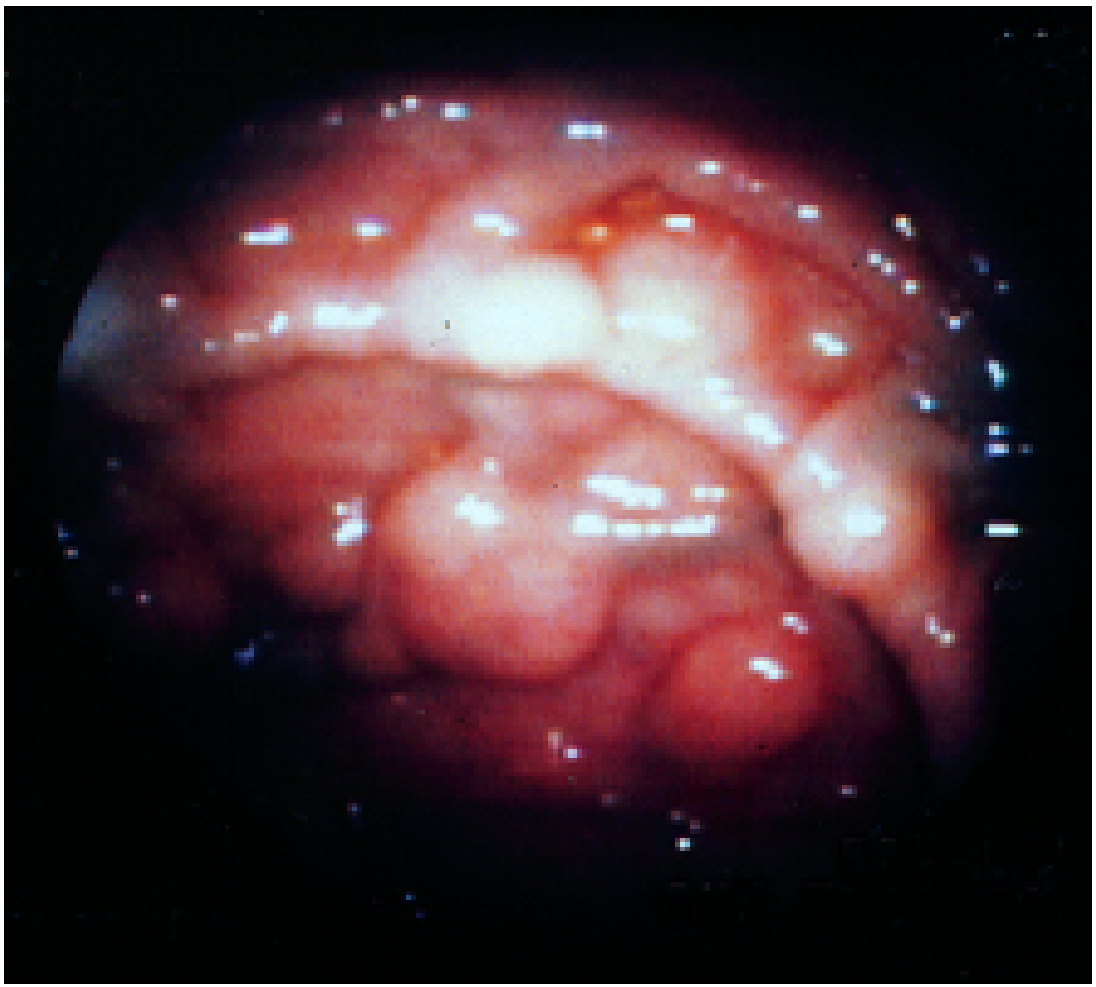
Diffuse Large B-cell Lymphoma

- 30-40% of all NHL
- Median age 65 yrs
- Increasing incidence
- Upto 40% present with only extranodal disease
- GI (stomach, ileocecal region) commonest EN site
- Rapid development of symptoms
- Potentially curable with multi-agent chemotherapy

Mantle Cell Lymphoma

- Aggressive B-cell lymphoma
- 7 % of all NHL
- Median age 60yr
- Widespread adenopathy, splenomegaly, EN
- GI tract involvement in 30% of cases at presentation
- Multi-agent chemotherapy
- Incurable (median survival 3 yrs)

Lymphomatous polyposis



Enteropathy-type T-cell lymphoma

- Uncommon
- Cell of origin: intraepithelial T-lymphocytes
- Seen in areas with a high prevalence of Coeliac disease (adult onset)
- Most commonly occurs in the Jejunum or ileum
- Abdominal pain and/or perforation
- HLA DQA1, DQB1 genotype
- Poor prognosis

GI lymphomas..summary

- Non-Hodgkin lymphomas are common and the incidence is increasing
- Gastrointestinal tract is a very common site of involvement
- Incisional biopsy allows for proper classification and treatment
- Resection of GI lymphoma is not recommended, unless necessary for diagnosis or management of acute complications (bleeding, perforation, obstruction)